

# Bacteriophage prehistory

## Is or is not Hankin, 1896, a phage reference?

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We identified 30 actual or presumptive “bacteriophage” references dating between the years 1895 and 1917 and have further explored one of the oldest: Hankin’s 1896 study of a bactericidal action associated with the waters of the Ganges and Jumna rivers in India. As Hankin’s work took place approximately 20 years prior to the actual discovery of bacteriophages, no claims were made as to a possible phage nature of the phenomenon. Here we suggest that it may be imprudent to assume nevertheless that it represents an early observation of phage-mediated bactericidal activity. Our principal argument is that the antibacterial aspect of these river waters was able to retain full potency following “heating” for one-half hour in hermetically sealed tubes, where heating in “open” tubes resulted in loss of antibacterial activity. We also suggest that environmental phage counts would have had to have been unusually high—greater than 10<sup>6</sup>/ml impacting a single host strain—to achieve the rates of bacterial loss that Hankin observed.

### Introduction

Traditionally, the discovery of bacteriophages is traced to the papers of Twort<sup>1</sup> and d’Hérelle.<sup>2</sup> Several earlier studies, however, hint at the existence of phage-like antibacterial activity. In his collection of phage references covering the years up to 1956, Raettig<sup>3</sup> lists no less than 28 pre-1918 reports. Two of these papers—Hankin (1896),<sup>4</sup> and Gildemeister (1917)—are discussed by d’Hérelle<sup>5</sup> and both he and Summers<sup>6</sup> cite a 29<sup>th</sup> authored

in 1901 by Emmerich and Löw. Summers also makes note of a “substantial literature on bacterial autolysis”, citing reference 7. A 30<sup>th</sup> such pre-1918 “prehistoric” phage paper, by Gameleya (1898), is both presented and, at least to a degree, refuted as a phage reference by Bardell.<sup>8,9</sup> Of all of these studies, only the paper by Twort<sup>1</sup> was published in English. Summers<sup>10</sup> provides a translation from French of the seminal phage article by d’Hérelle<sup>2</sup> and additional translations of this article have been published in *Research in Microbiology*<sup>11</sup> and *Bacteriophage*.<sup>12</sup>

In Table 1 we provide the references for all 30 of these presumptive (or actual) “bacteriophage” publications along with English translations of their titles. The bulk of the current study, however, consists of an exploration of one of the earliest published accounts of phage-like activity: Hankin’s 1896,<sup>4</sup> *Annales de l’Institut Pasteur* article, “L’action bactéricide des eaux de la Jumna et du Gange, sur le microbe du choléra”. We suggest, based especially on a lack of heat lability in sealed versus “open” tubes, that the antibacterial action observed by Hankin was *not* due to bacteriophages.

### Hankin, 1896

In 1896, the English chemist Ernest Hankin<sup>4,13</sup> published two articles in the *Annales de l’Institut Pasteur* describing microorganisms associated with rivers in India. The second of these articles,<sup>4</sup> “The bactericidal action of waters of Jumna and Ganges on the cholera microbe”, has been described by a number of authors as a very early description of the action

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**Table 1.** Pre-1918 presumptive phage references

Reference	English translation of title
Frankland P. Ueber das Verhalten des Typhusbacillus und des Bacillus coli communis im Trinkwasser. Zeitschrift für Hygiene und Infektionskrankheiten 1895; 19:393–407	On the behavior of the typhoid bacillus and the common Bacillus coli in drinking water
Hankin ME. L'action bactéricide des eaux de la Jumma et du Gange sur le vibron du choléra. Annales de l'Inst Pasteur 1896; 10:511–23	The bactericidal action of waters of Jumna and Ganges on the cholera microbe
Hankin ME. Les microbes des rivières de l'Inde. Annales de l'Inst Pasteur 1896; 10:175–6	The microbes of the rivers of India
Gamaleya NF, 1898. Бактериолизны—ферменты, разрушающие бактерий. Russ Arch Pathol Clin Med Bacteriol 6:607–13	Bacteriolysins-ferments destroying bacteria <sup>1</sup>
Emmerich R, Löw O. Bakteriolytische Enzyme als Ursache der erworbenen Immunität und die Heilung von Infektionskrankheiten durch dieselben. Zeitschrift für Hygiene und Infektionskrankheiten 1899; 31:1–65	Bacteriolytic enzymes as the cause of acquired immunity and cure for infectious diseases
Gamaleia. Bakteriolsine—bakterienzerstörende Fermente. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1899; 26:661–3 <sup>2</sup>	Bacteriolysins-bacteria-destroying enzymes
Emmerich R, Löw O. Die künstliche Darstellung der immunisierenden Substanzen (Nucleasen-Immunoproteidine) und ihre Verwendung zur Therapie die Infektionskrankheiten und zur Schutzimpfung an Stelle des Heilserums. Zeitschrift für Hygiene und Infektionskrankheiten 1901; 36:9–28	The artificial preparation of the immunizing substances (nuclease-immunoproteins) and their use in the treatment of infectious diseases and for vaccination in place of healing serum
Klein A. Die physiologische Bakteriologie des Darmkanals. Archiv für Hygiene 1902; 45:117–76	The physiological bacteriology of the intestinal canal
Krencker E. Über Baktericidie von Bakterienfiltraten. Inaug-Diss, Straßburg 1903	On the bactericidal activity of bacterial filtrates
Lode A. Experimentelle Untersuchungen über Bakterienantagonismus. I. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1903; 33:196–208	Experimental studies on bacterial antagonists. I
Eijkman C. Ueber thermolabile Stoffwechselprodukte als Ursache der natürlichen Wachstumshemmung der Mikroorganismen. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1904; 37:436–49	On the thermolabile metabolites as a cause of the natural growth inhibition of microorganisms
Conradi H, Kurpuweit O. Ueber spontane Wachstumshemmung der Bakterien infolge Selbstvergiftung. I. Muenchener Medizinische Wochenschrift 1905; 52:1761–4	On the spontaneous growth inhibition of bacteria due to self poisoning. I
Conradi H, Kurpuweit O. Ueber die Bedeutung der bakteriellen Hemmungsstoffe für die Physiologie und Pathologie des Darms. II. Muenchener Medizinische Wochenschrift 1905; 52:2164–8	On the importance of bacterial inhibition materials for the physiology and pathology of the intestine. II
Eijkman C. Ueber die Ursache der Wachstumshemmung in Bakterienkulturen. Berliner Klinische Wochenschrift 1906; 43:499	On the cause of growth inhibition in bacterial cultures
Eijkman C. Ueber natürliche Wachstumshemmung der Bakterien. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1906; 41:367-9 and 471–4	On the natural growth inhibition of bacteria
Manteufel. Untersuchungen über die „Autotoxine“ (Conradi) und ihre Bedeutung als Ursache der Wachstumshemmung in Bakterienkulturen. Berliner Klinische Wochenschrift 1906; 43:313–8	Studies on the “Auto toxins” (Conradi) and their importance as the cause of growth inhibition in bacterial cultures
Oebius R. Ueber spontane Wachstumshemmung der Bakterien auf künstlichem Nährboden. Medizinische Klinik 1906; 1906:598–601	On the spontaneous growth inhibition of bacteria on artificial media
Passini F. Die bakteriellen hemmungsstoffe Conrads und ihr Einfluss auf das Wachstum der Anaërobie des Darmes. Wiener klinische Wochenschrift 1906; 19:627–30	Conradi's bacterial inhibition materials and their influence on the growth of the anaerobic bacteria of the intestine
Rahn O. Ueber den Einfluss der Stoffwechselprodukte auf das Wachstum der Bakterien. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1906; 16:417–29	On the influence of metabolites on the growth of bacteria
Rolly [S.] Experimentelle Untersuchungen über das biologische Verhalten der Bakterien im Dickdarm. Deutsche medizinische Wochenschrift 1906; 32:1733-7.	Experimental studies on the biological behavior of the bacteria in the colon
Eijkman C. Ueber die Ursache der Wachstumshemmung in Bakterienkulturen. Deutsche medizinische Wochenschrift 1907; 33:265–6	On the cause of growth inhibition in bacterial cultures
Manteufel. Das Problem der Entwicklungshemmung in Bakterienkulturen und seine Beziehungen zu den Absterbeerscheinungen der Bakterien im Darmkanal. Zeitschrift für Hygiene und Infektionskrankheiten 1907; 57:337–54	The problem of resistance development in bacterial cultures and its relationship to the products of dying bacteria in the gut

**Table 1.** Pre-1918 presumptive phage references (continued)

Faltin R. Studien über Hetero- und Isoantagonismus, mit besonderer Berücksichtigung der Verhältnisse bei infektiösen Erkrankungen der Harnwege. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1908; 46:6–20	Studies on hetero- and isoantagonism, with special consideration of relationships in infectious diseases of the urinary tract
Remlinger P, Nouri O. Les géloses dites vaccinées. Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie 1908; 65:361–3	Inoculated agar media
Kantorowicz A. Bakterien-Antifermente und Bakteriolyse. Munchener Medizinische Wochenschrift 1909; 56:897–900	Bacterial fermentation inhibitors and bacterial lysis
de Waele H. Protéolase et antiprotéolase dans les cultures microbiennes. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1909; 50:40–4	Proteolytic enzymes and enzyme inhibitors in microbe cultures
Twort FW. An investigation on the nature of ultra-microscopic viruses. Lancet 1915; 2:1241–3	An investigation on the nature of ultra-microscopic viruses
Gildemeister E. Ueber Variabilitätserscheinungen des Typhusbacillus, die bereits bei seiner Isolierung aus dem infizierten Organismus auftreten. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1916; 78:209–25	Variability phenomena of the typhoid bacillus which already show up at the time of its isolation from the infected organism
d'Hérelle F. Sur un microbe invisible antagoniste des bacilles dysentériques. C R Acad Sci Ser D 1917; 165:373–5	On an invisible microbe antagonistic to the dysentery bacillus
Gildemeister E. Weitere Mitteilungen über Variabilitätserscheinungen bei Bakterien, die bereits bei ihrer Isolierung aus dem Organismus zu beobachten sind. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten 1917; 79:49–62	Further reports on the occurrence of variability in bacteria that is already observed at the time of their isolation from the (host) organism

<sup>1</sup>The title listed is the English translation provided by Bardell.<sup>8,9</sup> A direct translation is “Bacteriolysins-bacteria-destroying ferments”. See, however, the following footnote. <sup>2</sup>This is an overview of a number of Gamaleia/Gamaleya papers including the 1898 paper listed previously. The title listed with this entry is an English translation of the German.

of phages. For instance, from d'Hérelle<sup>14</sup> (p. 16), “To my mind there is no doubt that this antiseptic action ought in reality to be assigned to the bacteriophage.” In a later publication, however, d'Hérelle<sup>5</sup> seems to back down a little from this certainty, at least allowing for the possibility that (pp. 10–11) “if one wishes to hold the text of [Emmerich and Löw, 1901] to strict accountability and to take their statements literally it would be easy to demonstrate that it could not have been the bacteriophage which was involved, just as the bacteriophage could not have been the cause of the phenomenon observed by Hankin.”

Others have described Hankin's results also as possibly phage-related. For example, Hudson et al. state (p. 426), “The bactericidal activity of phages was first observed by Hankin in 1896”. From Parfitt<sup>16</sup> (p. 2,166), “The first inkling that phages existed came in 1896 when British chemist Ernest Hanbury Hankin discovered that the murky waters of the river Ganges could destroy cholera bacteria.” From Hanlon<sup>17</sup> (p. 1,050), “The concept of using phages in antibacterial therapy is not new. In 1896 Ernest Hankin observed that the Ganges and Jumna rivers in India seemed to possess antibacterial properties, and he surmised that this might in some way be responsible for the reduced number

of cases of gastrointestinal infection, particularly cholera, in those villages close to the river.” From Derisinski<sup>18</sup> (p. 1,096), “The use of phages for therapy of bacterial infection has its origin in an observation reported in 1896 by Ernest Hankin<sup>4</sup> of the presence of heat-labile, filterable antibacterial activity capable of killing *Vibrio cholerae* in the waters of the Ganges and Jumna Rivers.” From Atterbury<sup>19</sup> (p. 601): “...initial observations of these viruses date back to Hankin in 1896”. From Connerton and Connerton<sup>20</sup> (p. 311): “Bacteriophage were first reported in 1896 by Ernest Hankin...” And from Wei et al. (p. 3,247), citing Hankin, 1896 (ref. 4): “the lysis of *Vibrio cholerae* by a heat-labile substance in river water [was] the first evidence for the existence of bacteriophage...”

Other articles citing Hankin only claim that he observed some heat-labile substance, found in association with these river waters, that displayed bactericidal activity. That is, from Hankin<sup>4</sup> (p. 515), “It is seen that the unboiled water of the Ganges kills the cholera germ in less than 3 hours. The same water, when boiled, does not have the same effect. On the other hand, well water is a good medium for this microbe, whether boiled or filtered.” (“On voit que l'eau du Gange

non bouillie tue le microbe du choléra en moins de 3 heures. La même eau, bouillie, n'a pas la même action. L'eau de puits est, au contraire, un bon milieu pour ce microbe, qu'elle soit bouillie ou filtrée”). We explore here the consistency of the observations of Hankin, 1896, with the hypothesis that the bactericidal activity he observed could primarily have been a consequence of phage action.

### Checking on Plausibility

From the data provided by Hankin,<sup>4</sup> one can estimate the number of phages that would have to have been present to result in the levels of killing observed, if indeed the killing was due to phage presence. This we did by determining the number of bacteria remaining after one hour for each of the one-hour declines provided by Hankin ( $n = 45$ ) and then applying the equation  $P = -\ln(N_t/N_0)/(k60)$  where  $P$  is the phage density,  $N_t/N_0$  is the fraction of bacteria that survive after  $t = 1$  hour, 60 is 60 min, and  $k$  is the phage adsorption rate constant (for a rearranged version of the equation, see Appendix 4 in ref. 22). These calculated phage densities, all in excess of  $10^6/\text{ml}$  (Table 2), are plausible titers for aquatic environments but nonetheless are on the high

**Table 2.** Calculated phage densities based on rates of bacterial killing

Estimated <i>k</i> (ml/min):	Calculated phage densities (per ml):		
	Geometric mean	Arithmetic mean	Median
1.0 × 10 <sup>-9</sup>	1.8 × 10 <sup>7</sup>	2.4 × 10 <sup>7</sup>	2.0 × 10 <sup>7</sup>
2.5 × 10 <sup>-9</sup>	7.2 × 10 <sup>6</sup>	9.5 × 10 <sup>6</sup>	8.0 × 10 <sup>6</sup>
5.0 × 10 <sup>-9</sup>	3.6 × 10 <sup>6</sup>	4.7 × 10 <sup>6</sup>	4.0 × 10 <sup>6</sup>
1.0 × 10 <sup>-8</sup>	1.8 × 10 <sup>6</sup>	2.4 × 10 <sup>6</sup>	2.0 × 10 <sup>6</sup>

**Table 3.** Calculated phage densities post heating in sealed tubes versus unheated

Estimated <i>k</i> (ml/min):	Calculated phage densities following heating (per ml):			
	Geometric mean	Arithmetic mean	Median	No heating:
1.0 × 10 <sup>-9</sup>	3.6 × 10 <sup>7</sup>	4.0 × 10 <sup>7</sup>	1.8 × 10 <sup>7</sup>	2.8 × 10 <sup>7</sup>
2.5 × 10 <sup>-9</sup>	1.4 × 10 <sup>7</sup>	1.6 × 10 <sup>7</sup>	7.3 × 10 <sup>6</sup>	1.1 × 10 <sup>7</sup>
5.0 × 10 <sup>-9</sup>	7.2 × 10 <sup>6</sup>	8.0 × 10 <sup>6</sup>	3.7 × 10 <sup>6</sup>	5.5 × 10 <sup>6</sup>
1.0 × 10 <sup>-8</sup>	3.6 × 10 <sup>6</sup>	4.0 × 10 <sup>6</sup>	1.8 × 10 <sup>6</sup>	2.8 × 10 <sup>6</sup>

side for activity against a single bacterial type<sup>23</sup> (here *Vibrio cholerae*). Such discrepancies, especially between phage total counts and viable counts on specific indicator bacteria, have been described as the ‘Great-Plaque-Count-Anomaly’.<sup>24</sup>

Consistent with the possibility that phage counts might have been as high as those suggested in Table 2, various authors have explored theoretically the potential for phages to control *V. cholerae* populations in situ.<sup>21,25</sup> Das et al. however, determined vibriophage plaque counts in Indian freshwater bodies, but found counts of generally less than 10<sup>2</sup>/ml, a density not expected to have much impact on bacterial viability.<sup>27</sup> Faruque et al.<sup>27,28</sup> observed higher phage densities, though still less than 10<sup>4</sup>/ml. Note, however, that bactericidal phages could still be present at high densities but just not able to form plaques, i.e., limited in their ability to form progeny but still able to adsorb and kill bacteria. This is a possibility not usually explored in phage environmental studies. Alternatively, phage counts can decline in the course of enumeration<sup>29</sup> or might have been higher had different, hypothetically more permissive host bacteria been employed in the laboratory by these authors.

Notwithstanding these phage density issues, a compelling reason to suspect that phages are the cause of the observed bactericidal activity is a very phage-like specificity where the Ganges river water was not active against certain *V. cholerae*

strains, whereas the Jumna river water was. Similarly, the Jumna river was not active against “typhoid bacillus”. This specificity particularly can be a phage property. However, it is a property that can be less readily achieved if the presumptive phages consisted of multiple types—essentially representing a phage cocktail—rather than single strains. Also consistent with an association of the observed bactericidal action with phage activity is its heat lability, as Hankin demonstrated, though this consideration too is not as straightforward as superficially it may seem.

### “Heating” Water in Hermetically Sealed Tubes

Our key argument against the idea that these bactericidal agents are phages rests on subsequent experiments, performed by Hankin,<sup>4</sup> which form the basis of his suggestion that the agent is “volatile”. However, rather than showing that bactericidal agents could be found in volatiles, Hankin instead found that heating which was capable of eliminating bactericidal activity was not effective in eliminating that activity if the heated water were trapped in sealed tubes. From p. 519: “I heated the Jamuna water in hermetically sealed tubes; the water should lose all bactericidal properties if there is any destruction by heat, and retain these properties if this is due to any volatile substance that cannot escape, as the tube is opened only after cooling. It is the latter that was found

to occur...” (“j’ai chauffé de l’eau de la Jumna dans des tubes hermétiquement scellés ; elle doit perdre tout pouvoir bactéricide, s’il y a destruction par la chaleur, et le conserver, s’il est dû à une substance volatile qui ne peut plus s’échapper, le tube n’étant ouvert que lorsqu’il est froid. C’est ce dernier cas qui se réalise...”).

Key to interpreting this experiment is deciphering what Hankin<sup>4</sup> means by the word “chauffé”, that is, “heated”. He uses this word or equivalent in a number of places in the paper. For example, on p. 515: “chauffant dans l’autoclave” and “chauffage à l’autoclave”. He also notes near the beginning of p. 515 that “In this and the following experiments, the word ‘boiled’ refers to boiling at 115° in an autoclave for a half hour” (p. 515: “Dans cette expérience et les suivantes, le mot « bouilli » est l’abréviation de chauffé une demi-heure à 115° dans l’autoclave”). Thus, it would seem that the bactericidal agent had been exposed to substantial temperatures for substantial lengths of time. What we don’t know, of course, is how hot the liquid inside the sealed tube became, though keep in mind that phages are not endospores so should be susceptible to inactivation even following half-hour exposure to much lower temperatures than 115° (which we assume in any case to be in units Celsius since this temperature was used by Hankin to sterilize water in an autoclave).

Following this sealed heating, the waters reduced bacterial densities by the following per-hour amounts: 2,100→150→50; 1,500→50; 4,200→1,109; 3,500→100. These represent levels of bacterial survival of 0.07, 0.33, 0.03, 0.26 and 0.03, respectively. For *k* = 1.0 × 10<sup>-9</sup> ml/min then 0.07 bacterial survival after one hour would imply a phage density, *P*, of -ln(0.07)/(10<sup>-9</sup> × 60) = 4.4 × 10<sup>7</sup>/ml. Using calculations such as these, in Table 3 we repeat the exercise presented in Table 2 but using the above-indicated bacterial one-hour survival values. This estimation of phage densities compares with a single unheated but filtered killing-positive control where bacterial density dropped from 4,200 to 800 in one hour (0.19 bacterial survival; see last column, Table 3). Note that heating the bactericidal waters for one-half hour in “open” rather than hermetically



sealed tubes reduced bactericidal action to effectively zero.

## Conclusion

D'Hérelle<sup>5</sup> seems to find fault in Hankin's evidence that the bactericidal agent is "volatile", suggesting that generally evidence of phage volatility is found wanting because (p. 8) "when distillation is carried out at low temperatures, without special precautions, materials are carried over into the distillate". This is an odd argument, however, because Hankin, as we have seen, did not show that phages were volatile but instead that the bactericidal agent was not destroyed by heating within a sealed container. Despite D'Hérelle's objections, we therefore stand by our assertion that while Hankin<sup>4</sup> clearly appears to have discovered a bactericidal property associated within Indian river water, Hankin's experiments seem to be inconsistent with that property being due to the presence of phages. Notwithstanding this skepticism, we are unable to identify an alternative hypothesis other than to speculate that some volatile bactericidal chemical agent, active against some bacterial strains but not others, must have been present in the waters Hankin tested.

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